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Short communication

# Comparison of sleep and other non-motor symptoms between SWEDDs patients and *de novo* Parkinson's disease patients

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ABSTRACT

*Background:* SWEDDs (Scans Without Evidence of Dopaminergic Deficits) was defined from a series of pharmaceutical trials on Parkinson's disease (PD). Non-motor features including sleep-related problems are common even in early-stage PD patients; however, little is known about the burden of the non-motor symptoms in SWEDDs patients.

*Methods:* The Non-motor Symptoms Assessment Scale (NMSS), revised version of the Parkinson's Disease Sleep Scale (PDSS-2), Epworth Sleepiness Scale (ESS), and EuroQol 5-Dimension (EQ-5D) were applied to evaluate 17 SWEDDs patients and 28 *de novo* PD patients. The presence of clinically probable rapid eye movement sleep behavior disorder (cpRBD) was assessed using the International Classification of Sleep Disorders-Revised (ICSD-R) criteria.

*Results:* The total NMSS score for the SWEDDs group was significantly lower than for the *de novo* PD group ($p = 0.032$). The most distinct difference was in taste or smell change ($p < 0.000$). Prevalence of cpRBD was higher in *de novo* PD patients than in SWEDDs patients ($p = 0.030$), though no significant differences in the PDSS-2 total score ($p = 0.496$) or the ESS score ($p = 0.517$) were found. The SWEDDs patients did not significantly differ from the *de novo* PD patients with regard to quality of life, as measured by the EQ-5D index score ($p = 0.177$).

*Conclusions:* The patients with SWEDDs have less non-motor problems than newly diagnosed untreated PD patients. Given the difficulty distinguishing between SWEDDs and early PD, identifying some of non-motor symptoms, such as RBD or olfactory impairment, could aid clinicians in their work.



## 1. Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease diagnosed by its cardinal symptoms, including bradykinesia, resting tremor, rigidity and postural instability. The symptoms of PD are linked to dysregulated nigrostriatal neurotransmission, which shows asymmetric deficits in quantitative dopaminergic radiotracer imaging [1,2]. However, a proportion of patients with a clinical diagnosis of PD in recent clinical trials, but with normal nigrostriatal dopaminergic imaging results, were reported [2,3]. These unexpected patients were designated as subjects with scans without evidence of dopaminergic deficit (SWEDDs), and their exact pathobiology remains intriguing [1–5].

In terms of the non-motor manifestations of SWEDDs patients, a few studies have shown that the olfactory test [4], cardiac sympathetic denervation [5], and anxiety-depression scales [3] are possible dimensions for clinical differentiation of PD and SWEDDs. Most studies on SWEDDs to date, however, have focused on the quantitative or qualitative motor symptoms, and there is still limited data on non-motor symptoms of SWEDDs [1–3]. In particular, the differences in comprehensive sleep-related problems including rapid eye movement sleep behavior disorder (RBD) and excessive daytime sleepiness (EDS) have hardly been discussed, despite sleep disturbance being reported as one of the non-motor symptoms most closely associated with diminished QoL in early-stage PD patients [6,7]. Furthermore, some of the non-motor

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manifestations, such as depression, pain, or urinary dysfunction, can be alleviated by pro-dopaminergic therapy. In contrast, sleep attack, hallucination, psychosis, and orthostatic hypotension are known to be aggravated by dopaminergic replacement therapy [8]. Consequently, a comparison of the non-motor manifestations in untreated *de novo* PD patients with those of SWEDDs patients was necessary. To the best of our knowledge, no previous study has compared non-motor symptom constellations of drug-naïve PD patients versus SWEDDs patients [3–5]. To avoid the possible confound of dopaminergic treatment, our study compared the non-motor symptoms in SWEDDs patients with newly diagnosed untreated PD patients.

## 2. Methods

### 2.1. Patients

This cross-sectional study prospectively involved 45 subjects who were referred to our academic movement disorders center. They had all been referred to us with a presumptive diagnosis of idiopathic PD made by their neurologist. The patients underwent clinical reassessment by the study investigators, and all included subjects met the diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank. Patients with vascular parkinsonism, atypical parkinsonian syndrome, dementia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria or patients <40 years old were excluded.

Dopamine transporter (DAT) scans of the patients were inspected by independent nuclear medicine clinicians as part of the routine clinical practice. According to the results of $^{123}$I-β-CIT or $^{18}$F-FP-CIT scans, the patients were divided into two groups, the SWEDDs group or the *de novo* PD group. Seventeen SWEDDs patients, who had an initial clinical diagnosis of PD and presented normal DAT scan results, were recruited for this study eventually. Twenty-eight *de novo* PD patients who were clinically diagnosed with PD and whose DAT scans showed a corresponding dopaminergic deficit were recruited. DAT scans were ordered by the study investigators in 15 of 17 SWEDDs patients (88.24%) and in 25 of 28 *de novo* PD patients (89.29%). Two of 17 SWEDDs patients (11.76%) and Three of 28 *de novo* PD patients (10.71%) arrived with outside DAT scans. Two of 17 SWEDDs patients (11.76%) had previously taken dopaminergic medication and had been withdrawn of antiparkinsonian therapy due to an absent response. None of the newly diagnosed PD patients had previously taken dopaminergic drugs (drug-naïve). Written informed consent was obtained from all patients participating in this study. All procedures and analyses of this study were approved by the Institutional Review Board at the Seoul National University Hospital.

### 2.2. Assessments

Demographics and basic clinical characteristics were obtained from all subjects. Parkinsonian motor symptoms were rated using the Unified Parkinson's Disease Rating Scale (UPDRS) part III. Non-motor features were addressed with the 30-item Non-motor Symptoms Scale (NMSS) which is organized into nine domains: cardiovascular, sleep-fatigue, mood-apathy, perception, attention/memory, gastrointestinal, urinary, sexual problems, and miscellaneous [7]. We administered the revised version of the Parkinson's Disease Sleep Scale (PDSS-2) and the Epworth Sleepiness Scale (ESS) to quantify a range of sleep-related problems in our study patients [9]. Then, the items of the PDSS-2 were grouped into three relevant subdomains: motor symptoms at night (items 4, 5, 6, 12 and 13), PD symptoms at night (items 7, 9, 10, 11 and 15), and disturbed sleep (items 1, 2, 3, 8 and 14). The symptoms of EDS were measured using the responses to the 8-item ESS, in which score of >10 was considered positive for EDS [9]. Clinically probable RBD (cpRBD) was defined according to the International Classification of Sleep Disorders-Revised (ICSD-R) minimal diagnostic criteria [10]. In accordance with the ICSD-R criteria, the diagnosis of cpRBD was based on the information of patients collected by clinical interviews undertaken by the movement disorders neurologist (H.-J.Y.). If available, family members or care givers accompanying patients were also asked about patients' nocturnal symptoms during the interviews with patients.

Health-related QoL was investigated using the generic EuroQol 5-Dimension (EQ-5D) instrument [7,11]. The EQ-5D consists of five different sub-dimensions of health attributes (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) and presents a preference-weighted EQ-5D index score which ranges from 0.00 to 1.00, with 1.00 being optimal health. The EQ-5D index score was calculated using the time trade-off method, based on a recent study performed for the Korean population [11].

### 2.3. Statistical analysis

In categorical variables, either chi-square test or Fisher's exact test was conducted as appropriate. Other variables were examined using the non-parametric Mann–Whitney *U* test. The results were considered statistically significant at $p < 0.05$ (IBM SPSS version 19; IBM corporation, Somers, NY). In consideration of the explorative nature of this study, we did not adjust for multiple comparisons.

## 3. Results

Table 1 shows the demographic and clinical data of SWEDDs versus *de novo* PD patients. Gender distribution of patients enrolled in the two groups did not differ significantly, but the SWEDDs group was older.

Fig. 1A shows the differences in the NMSS total and domain scores for SWEDDs versus *de novo* PD patients. The total NMSS score for the SWEDDs group was significantly lower than for the *de novo* PD group (mean ± standard deviation, 23.0 ± 16.2 vs. 38.3 ± 25.0, respectively; $p = 0.032$). Symptoms in the gastrointestinal domain ($p = 0.047$) and the miscellaneous domain ($p = 0.001$) were significantly greater among the *de novo* PD patients than among the SWEDDs patients (Fig. 1A). In each item of the NMSS, the most distinct difference in score was identified in taste or smell change, which was 2.43 (SD: 2.57) in *de novo* PD but only 0.12 (SD: 0.33) in SWEDDs ($p < 0.000$, Supplement Table 1).

Fig. 1B illustrates sleep-related problems in the two groups. All patients made available cohabiting family members or care givers for sleep-related problems interview. The prevalence of cpRBD was lower in SWEDDs patients than *de novo* PD patients (17.6% vs. 50.0%; $p = 0.030$). However, the SWEDDs patients did not differ significantly from the *de novo* PD patients with regard to the PDSS-2 total score (10.53 ± 7.26 vs. 11.68 ± 6.04, respectively; $p = 0.496$). No significant difference was observed in any PDSS-2 subdomain: motor symptoms at night ($p = 0.436$), PD symptoms at night ($p = 0.296$), or disturbed sleep ($p = 0.805$). The total ESS scores were 4.58 (SD: 2.40) for the SWEDDs patients and 5.39 (SD: 3.39) for the *de novo* PD patients, which were not statistically different ($p = 0.517$). There were no considerable differences between two groups in the prevalence of EDS when measured by an ESS score >10 ($p = 0.517$). Only two of 28 *de novo* PD patients (7.14%) and none of 17 SWEDDs patients had ESS scores over 10.

Patient-reported health-related QoL measured by the EQ-5D demonstrated no statistically significant differences between the two groups using Korean preference weights ($p = 0.177$) [11]. No considerable difference between the groups was observed in any of the EQ-5D sub-dimensions (Table 1).

**Table 1**
Demographics, clinical features, and health-related quality of life of SWEDDs and *de novo* PD patients.

| Characteristics | SWEDDs patients ($n = 17$) | *de novo* PD patients ($n = 28$) | *p*-value |
|---|---|---|---|
| Females, *n* (%) | 7 (41.2) | 11 (39.3) | 0.572 |
| Age (years) | 69.1 (8.1) | 62.9 (7.7) | 0.020* |
| Age at onset (years) | 65.9 (8.1) | 61.3 (8.0) | 0.122 |
| Disease duration (years) | 3.3 (2.6) | 1.4 (0.8) | 0.001* |
| UPDRS motor score | 9.3 (5.3) | 20.3 (9.1) | <0.000* |
| EQ-5D index score | 0.75 (0.24) | 0.66 (0.19) | 0.177 |
| EQ-5D sub-dimensions | | | |
| Mobility | 1.19 (0.47) | 1.50 (0.51) | 0.180 |
| Self-care | 1.24 (0.44) | 1.39 (0.48) | 0.282 |
| Usual activity | 1.29 (0.47) | 1.57 (0.50) | 0.074 |
| Pain/discomfort | 1.59 (0.62) | 1.64 (0.56) | 0.699 |
| Anxiety/depression | 1.47 (0.51) | 1.54 (0.51) | 0.675 |

Data are shown as means (standard deviation) or number (%). *Significance level: $p < 0.05$. *p*-values are from the chi-square test, Fisher's exact test or Mann–Whitney *U* test, as appropriate. EQ-5D index score: range 0.00–1.00, where 1.00 represents optimal health. EQ-5D sub-dimension scores: 1 = no problem, 2 = moderate, 3 = severe. EQ-5D, EuroQol 5-Dimensions; PD, Parkinson's disease; SWEDDs, Scans without evidence of dopaminergic deficit; UPDRS, Unified Parkinson's Disease Rating Scale.

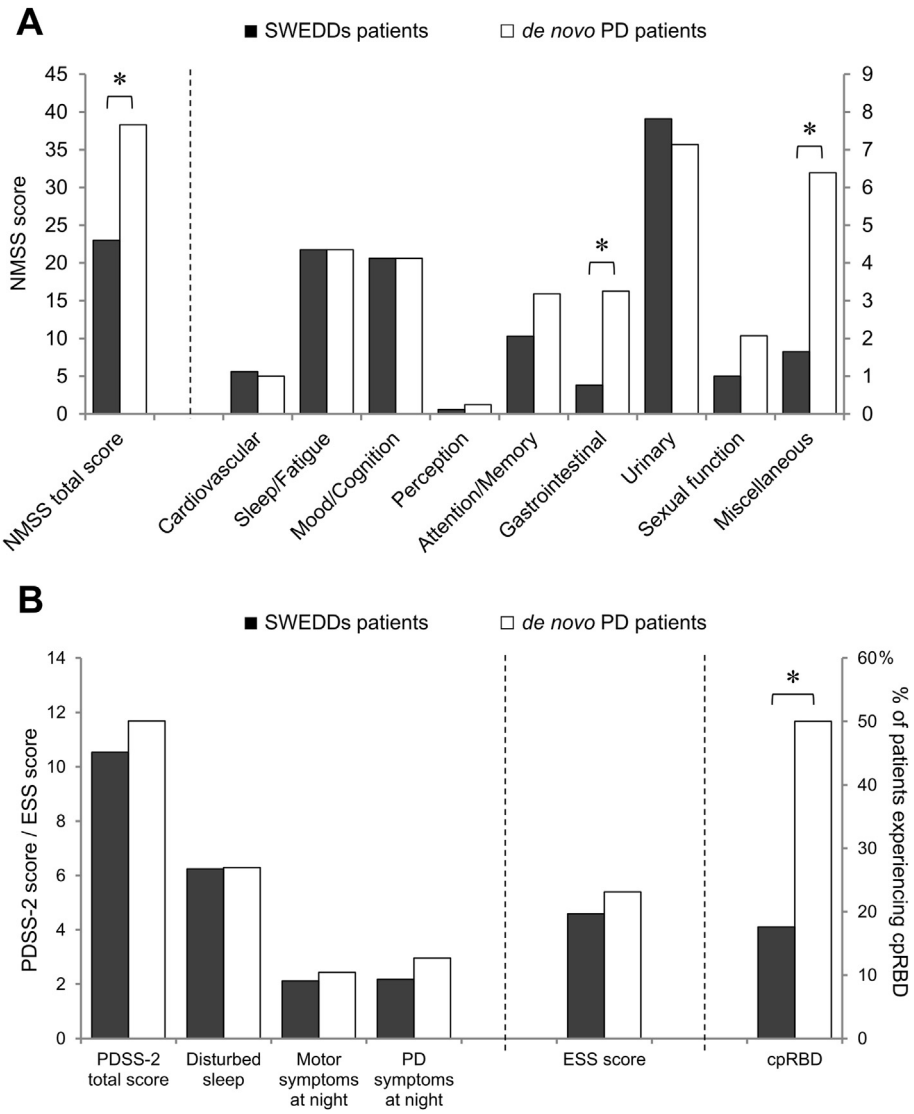


**Fig. 1.** A–B: (A) The Non-motor Symptoms Scale (NMSS) total and domain scores for scans without evidence of dopaminergic deficit (SWEDDs) versus *de novo* Parkinson's disease (PD) patients. (B) Comparison of sleep-related problems for SWEDDs patients and *de novo* PD patients. *Significance level: $p < 0.05$, the chi-square test, Fisher's exact test or Mann–Whitney *U* test, as appropriate.

## 4. Discussion

In the current study, non-motor symptoms as measured by the NMSS were greater in drug-naïve PD patients than in SWEDDs patients, which corroborate the results from previous non-motor studies examining SWEDDs versus pro-dopaminergic treated PD patients [3–5]. Significant differences by domain were observed in the scores of the miscellaneous domain, particularly taste and olfactory change, and of the gastrointestinal domain (Fig. 1A, Supplement Table 1).

Regarding sleep-related problems, cpRBD was more frequently reported in *de novo* PD patients as expected [9,12]. However, our study did not find significant differences in the PDSS-2 or its subdomain scores between the two groups. In addition, there were no statistically significant differences in daytime somnolence as assessed by the ESS score. The discrepancy with the findings of a previous report [5], which shows significant differences in daytime sleepiness, might depend on the different subjects examined (unmedicated *de novo* PD subjects versus pro-dopaminergic treated PD subjects), or on the use of different scales. Our study utilized the established instrument of ESS based on the reported cut-off value [9], whereas the previous study used a single item of the NMSS (question #3) only [5].

One notable feature of our results is that RBD and olfactory impairment, which showed considerable differences here, are known to be the early-stage non-motor feature or premotor symptoms which can precede overt PD by years [12]. In contrast to the similarity of motor symptoms between SWEDDs and *de novo* PD, the differences in the early-stage non-motor constellations provide compelling evidence that different pathobiological mechanisms are involved [3,12].

One unanticipated finding was the lack of a significant difference in the EQ-5D scores between the two groups, although there was a tendency for impaired QoL in *de novo* PD patients [7]. We expected greater impairment in QoL in the drug-naïve PD group, because the patients of this group were hampered by more motor and non-motor symptoms [6,7]. There are several possible explanations for the EQ-5D result. First, depression and anxiety were reported psychological determinant related to QoL in patients with PD, and previous studies on the impact on QoL of non-motor

symptoms in early-stage PD most closely related insomnia, excessive daytime somnolence, memory complaints, anxiety and depression to diminished QoL [6]. In our study, however, these non-motor domains showed little difference between the two groups. Disease burden as measured by the EQ-5D would demonstrate no differences accordingly. Another possible explanation for our results is the utilization of disease-nonspecific generic QoL instruments, instead of disease-specific instruments. Our research did not apply disease-specific QoL scales, such as the Parkinson's Disease Questionnaire (PDQ-39) or its short-form (PDQ-8), but instead used the EQ-5D, a widely-used generic QoL instrument [7,11]. Although the EQ-5D is a validated generic QoL tool, and is recommended by a recent systematic review on health-related QoL in PD patients [7], minor differences in QoL may not sufficiently be captured by the disease-nonspecific instruments. In addition, the absence of significant differences in QoL measurements may be due to the relatively small sample size in our study.

Our finding needs to be interpreted with caution based on several limitations. One such limitation of this study is its questionnaire-based design with the absence of the objective confirmation test, such as, polysomnographic evidence or olfactory function test. Other limitations include the small number of subjects and the cross-sectional study design without the pathological confirmation, which may influence the generalizability of these data. Larger replication studies with a healthy-control group using a disease-specific QoL instrument and a objective confirmation test of non-motor symptoms are needed to verify our result.

SWEDDs has received much attention in recent decades, not only due to its importance in daily practice, but also for its significances in neuroprotective clinical trials, research studies into the genetics and epidemiology of PD as well as biomarker research in early-stage of disease [1–3]. Given the difficulty distinguishing between SWEDDs and early PD using motor symptoms, the brief screening of some early-stage non-motor features, such as RBD or olfactory impairment, could be beneficial for clinical practice.

## Conflict of interest

The author has no conflicts of interest to declare.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.09.024.

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